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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,396	03/20/2002	Yoon S. Cho-Chung	214616	7877

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LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6780

EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,396	CHO-CHUNG, YOON S.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *September 6 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *September 6, 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Amendment and Declaration filed September 6, 2005 in response to the Office Action of June 2, 2005 are acknowledged and have been entered. Previously pending claims 3 and 6 have been amended. Claims 9-20 have been canceled and claims 1-8 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are maintained:

Claim Rejections - 35 USC § 112

4. Claims 1-8 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in the paper mailed June 2, 2005, Section 4, pages 3-14.

Applicant states that the Office does not dispute that the claimed method is enabled as to the assay for ECPKA activity. Examiner notes, in order to clarify the record, that the Office specifically states that the claimed method is enabled for the diagnosis of carcinoma in a patient comprising assaying a fluid sample from the patient for increased phosphorylation activity. Contrary to Applicant's assertion, the Office does not state that the invention, as stated by Applicant is enabled.

Applicant argues that the Office's rejection of the claims drawn to diagnosis methods comprising assaying expression level of ECPKA reflects a fundamental misconception of the claimed invention. In particular, ECPKA is extracellular PKA whereas other forms of PKA are intracellular or are membrane bound PKA (i.e. ecto-cellular) thus one can distinguish between ECPKA and PKA expression levels on the basis of whether an assay was performed on the extracellular or cellular fraction of a sample and points specifically to page 9, lines 25-30 of the specification. The argument has been considered but has not been found persuasive

because Applicant is arguing limitations not recited in the claims as currently constituted. Applicant is reminded that although the claims are interpreted in light of the specification, limitations recited in the specification are not read into the claims. Further, a review of page 9, lines 25-30 reveal teachings drawn to standard PKA ELISA assays of cells wherein the extent of cell lysis should be assessed to accurately distinguish ECPKA from intracellular PKA. The teaching however, does not teach how to distinguish ECPKA from membrane bound PKA. In addition, the teaching suggests using antibody to the catalytic subunit or the regulatory subunit of ECPKA for apparently determining the concentration of ECPKA. However, in light of the teaching in the specification and the submitted post-filing reference, Cho et al, PNAS, it is clear that the concentration of ECPKA cannot be determined by using antibody to the regulatory subunit of ECPKA since the Cho et al reference specifically teaches that "PKA (ECPKA) is present in active, free catalytic subunit (C subunit) form" (see abstract) and is clearly not associated with a regulatory subunit. Although Applicant suggests that the assay can be performed using antibodies to the catalytic subunit of PKA, this suggestion does not remedy the deficiencies of the teaching of the specification because the teaching does not distinguish between ECPKA, membrane bound PKA and PKA from the inevitably lysed cells in the sample which, because of endogenous camp would be expected to include active catalytic subunits.

Applicant points to a post-filing reference (Cho et al, PNAS, 2000, 97:835-840) for enablement of the claimed invention drawn to any sample, wherein the reference teaches that PKA exists in all cells as an inactive holoenzyme, that is with a C subunit bound with an R subunit whereas ECPKA exists as a C subunit only therefore it is active in the absence of exogenous cAMP. The argument has

been considered but has not been found persuasive because the claims are drawn to assaying elevated level of ECPKA and for the reasons of record, a predictable nexus between ECPKA activity and level has not been established.

Applicant argues that the specification provides structural characteristics of ECPKA wherein ECPKA is detected using antibodies to the "C" catalytic subunit of PKA, demonstrating that the catalytic subunit of ECPKA is structurally similar to the known catalytic subunit of PKA. Knowledge of the exact structure of ECPKA or the differences between ECPKA and other forms is PKA is not required to meet the enablement standard. All that is required is sufficient guidance to allow one of ordinary skill in the art to make and use the claimed invention. The argument has been considered but has not been found persuasive because a review of page 9, lines 25-30 reveal teachings drawn to standard PKA ELISA assays of cells wherein the extent of cell lysis should be assessed to accurately distinguish ECPKA from intracellular PKA. The teaching however, does not teach how to distinguish ECPKA from membrane bound PKA or even PKA from lysed cells, thus it appears that critical to the claimed invention in samples, other than body fluid samples, is the ability to distinguish between ECPKA and other forms of PKA. However, although the specification specifically teaches that monoclonal antibodies that distinguish ECPKA from intracellular and ectoPKA can be generated in accordance with methods known in the art, the submitted post-filing reference by Cho et al, PNAS specifically teaches that ECPKA is immunologically and biochemically identical to the intracellular PKA catalytic subunit Calpha (p. 839, col 2). Given that teaching it is clearly not possible to distinguish between ECPKA and the catalytic subunit C alpha of intracellular or ectoPKA. Since, according to the post-filing reference, it is not possible to distinguish between

ECPKA and the intracellular PKA Calpha, it is not clear how one would predictably diagnose cancer in a patient by assaying for ECPKA by simply assaying for the PKA catalytic subunit in any sample. As previously set forth, Applicant is claiming a functional equivalent of intracellular PKA. The specification teaches what ECPKA does, but does not teach what it is and this teaching does not enable the claimed invention.

Applicant argues that the Office provides no evidence that mechanisms distinct from overexpression are responsible for increased kinase activity and the disclosure by the Office of CDK4 and SRC which show increased activity by various mechanisms, other than overexpression, by which kinase activity can be increased is not relevant since the references are not drawn to ECPKA. The argument has been considered but has not been found persuasive because contrary to Applicant's argument, Examiner does not state that mechanisms distinct from overexpression are responsible for increased kinase activity, but rather states that the cause of increased activity cannot be determined from the specification and because of the lack of guidance in the specification, it cannot be predicted that ECPKA protein has an elevated level. As previously set forth, a wide variety of alterations in the enzymes, their cofactors and effectors lead to unregulated activity and are known in the art. Examiner's disclosure is exemplified by numerous references. Although PKA is not among the references, it is clear that PKA also is subject to its cofactors and effectors and nothing in the specification, as originally filed provides a specific nexus between overexpression of ECPKA and increased enzyme activity.

Applicant further argues that ECPKA expression is regulated by PKA expression which strongly suggests that enhanced ECPKA activity is linked to

enhanced ECPKA expression, which outweighs the evidence presented by the Office. Applicant points specifically to page 3, lines 10-18 and Example 7 The argument has been considered but has not been found persuasive because a review of page 3 lines 10-18 reveals only that enhanced expression of Ri alpha/PKA-1 has been shown in cancer cell lines and primary tumors and a review of Example 7 reveals only that ECPKA is immunologically related to intracellular PKA. Thus, contrary to Applicant's argument, the support cited does not suggest that enhanced ECPKA is linked to enhanced ECPKA expression.

Applicant argues that Weber et al do not show an absence of ECPKA in renal cell or CLL. The argument has been considered but has not been found persuasive. The specification clearly discloses that ECPKA has been surprisingly and unexpected discovered (p. 3) and further teaches that antibody that distinguishes ECPKA from intracellular PKA and ectoPKA can be generated (p. 20). Given that teaching and the teaching that distinguishing antibody to either R subunit or C subunit can be made by methods known in the art, the specification infers that ECPKA is a novel protein. The discussion of Weber et al was drawn to the novel R subunit inferred by the specification. It appears that Applicant is admitting on the record that, contrary to the teaching in the specification, that ECPKA is not associated with any R subunit, novel or otherwise.

Aplicant further argues that the examples and additional evidence submitted in the Cho Declaration demonstrate that ECPKA activity is elevated in a wide variety of cancer cells. This argument has been considered but has not been found persuasive. The specification demonstrates that conditioned medium of cultured cancer cell lines and serum of cancer patients contain PKA kinase activity. The Declaration states that ECPKA activity levels were measured in a variety of cancer

cells using the PKA assay disclosed in Example 1 and that several different carcinoma cell types were tested along with three sarcoma cell lines. The Declaration includes lists of samples and PKA activity. The argument and Declaration have been considered but have not been found persuasive. Since the Declaration states that the method used was that of Example 1, it can only be assumed that the cells tested might be cancer cell lines and that it was the conditioned medium that was tested for activity. However, the rejection is not based on activity per se, but rather the rejection is based on the inability of correlating activity to increased presence of ECPKA. Further, even if it were to be found that concentration is positively related to ECPKA protein presence, it is not possible for Examiner to determine whether indeed there is a differential in activity in what appears to be conditioned medium of the cell lines and normal cells since no normal cells are disclosed. Although Applicant states that ECPKA activity was elevated in sarcoma samples as compared to average ECPKA level of 12.2 mU/ml observed in normal cells, applicant does not state that the normal cells were muscle, nerve or connective tissue cells, thus the data cannot be evaluated because it is unclear whether or not the "normal cells" were cells of the same lineage as the sarcoma samples. Further, given that claims 3 and 6 are specifically drawn to an activity level of normal controls from about 0-1.0mUnits/ml blood serum, the finding of 12.2 mU/ml for the normal control for ECPKA is at a minimum confusing. Although it is not clear what the normal controls are (or where they were found), given the high level of activity, it appears that these normal cells would be diagnosed as cancer cells since claims 3 and 6 require that the control sample is from about 0 to about 1.0 mUnits/ml blood serum.

Applicant further argues that a solid sample can be used by fractionating the sample to remove the cellular component or cells could be cultured and then the medium tested for PKA activity. The argument has been considered but has not been found persuasive since the claims are drawn to determining an elevated presence of ECPKA and for the reasons of record no nexus has been established between activity level and presence of elevated levels of ECPKA.

Applicant argues that experimental evidence is submitted in the form of the Cho Declaration that demonstrates that sarcomas can be diagnosed with the claimed method without undue experimentation. The argument has been considered but has not been found persuasive. Although the Cho Declaration discloses the ECPKA activity of cell lines, for the reasons set forth above, the information cannot be evaluated since the "normal cells" assayed are not defined. Further, it is not possible to determine from the information in the Declaration whether the sarcoma cells lines are overexpressing endogenous PKA or whether they have been transfected to constitutively express PKA. Further, as set forth above, the activity assay does not provide a predictable nexus to elevated levels of PKA for the reasons of record.

Applicant argues that it is well within the skill of the ordinary artisan to diagnose a particular type of cancer in conjunction with the claimed method and the specification discloses markers for cancers and well known methods. The argument has been considered but has not been found persuasive because as previously set forth, although the claims are read in light of the specification, limitations in the specification are read into the claims. The claimed invention cannot be used to diagnose the specific cancers as claimed for the reasons of

record. The argument has been considered but has not been found persuasive and the rejection is maintained.

5. Claims 1-8 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in the paper mailed June 2, 2005, Section 5, pages 14-15.

Applicant argues that the claims are not directed to ECPKA per se. The argument has been considered but has not been found persuasive because, as previously set forth, in the absence of a written description for a product, the method of using said product is not adequately described.

Applicant argues that the structure of relevant portions of ECPKA and its function are described. That is, it exists in the free C subunit form, that it is structurally related to the C subunit of other forms since antibodies to the C subunit of PKA can also be used to detect ECPKA, that it uses kemptide for its catalytic activity and further the specification discloses a direct correlation between the similarity in the structure of ECPKA to PKA with a similarity in catalytic function. The argument has been considered but has not been found persuasive. Although the specification teaches that the kemptide assay is useful for ECPKA and that antibodies to the C subunit also detect ECPKA, the specification also teaches that ECPKA is distinguishable from intracellular PKA and ectoPKA using antibodies against ECPKA. However, the specification does not teach which portions of ECPKA can be used to produce the distinguishing antibodies, does not teach the structure of ECPKA which has been newly and surprisingly discovered by Applicant. Further, as previously set forth, Applicant is claiming a functional equivalent of intracellular PKA. The specification teaches what ECPKA does, but does not teach what it is and this teaching does not enable the claimed invention.

The argument has been considered but has not been found persuasive and the rejection is maintained.

6. Claims 1-8 rejected under 35 USC 112, second paragraph for the reasons previously set forth in the paper mailed June 2, 2005, Section 6, pages 16.

Applicant argues that claim 1 defines ECPKA and that thus ECPKA is not a laboratory designation and that the term is defined in claim 1 as extracellular camp-dependent protein kinase and the limitation "extracellular is sufficient to distinguish the claimed subject matter. The argument has been considered but has not been found persuasive because surprisingly discovered PKA is not defined by the specification nor the claims for the reasons of record and for the reasons set forth above. The argument has been considered but has not been found persuasive and the rejection is maintained.

7. All other objections and rejections set forth in the previous paper are hereby withdrawn.

8. No claims allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
October 24, 2005